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<p>(21) International Application Number: PCT/GB97/03102</p> <p>(22) International Filing Date: 12 November 1997 (12.11.97)</p> <p>(30) Priority Data: 9623833.2 16 November 1996 (16.11.96) GB</p> <p>(71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HEDGE, Philip, John [GB/GB]; (GB). BOYLE, Francis, Thomas [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).</p> <p>(74) Agent: TINSLEY, Rachel, Maria; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: RAF KINASE INHIBITORS</p> <div data-bbox="418 1075 1185 1333" data-label="Chemical-Block"> <p style="text-align: right;">(I)</p> </div> <p>(57) Abstract</p> <p>The present invention relates to pharmaceutical compositions comprising inhibitors of raf kinase of formula (I) wherein: R¹ and R² are substituents on the phenyl rings; p, which may take the same or different values for R¹ and R², is 0-3, and when p is 2 or 3 each group may be the same or different; R³ is C₁₋₄alkyl; q is 0-4; R⁴ is aryl or cycloalkyl wherein R⁴ is optionally substituted with up to 3 substituents or a pharmaceutically acceptable salt or <i>in vivo</i> hydrolysable ester thereof and a pharmaceutically acceptable carrier with the proviso that N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-cyclopentylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-phenylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(2-cyclohexylacetylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-aminobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxymethylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-3-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]benzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide and N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide are excluded. Processes for their preparation and their use as therapeutic agents. A particular use is in cancer therapy.</p>		

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RAF KINASE INHIBITORS

This invention relates to compounds that inhibit the enzyme raf kinase (raf), an enzyme which acts downstream of ras and plays a crucial role in transduction of signal
5 towards the nucleus. The invention also relates to methods of manufacturing the compounds, pharmaceutical compositions and methods of treating diseases, especially cancer, which are mediated through raf kinase activity.

Oncogenic forms of ras are found in 30% of all cancers, including colon (50%), lung (30%) and pancreas (90%). Mutated, oncogenic forms of the ras GTP-binding proteins are
10 insensitive to activation of their intrinsic GTPase activity and therefore locked in an active form, constitutively activating downstream components of a mitogenic signalling pathway. Several groups simultaneously demonstrated that ras binds directly to the product of the raf proto-oncogene, c-raf-1, thus implicating raf as an effector of ras mediated signalling (Cell (1993) 74, 308-313). Raf lies at the top of a kinase cascade which results in activation of
15 MEK (Map kinase kinase) and then MAP-kinase and subsequent transcriptional activation of genes involved in cell proliferation. This, coupled with previous evidence that raf is an essential downstream component of ras signalling and is itself oncogenically transforming when in a constitutively active form, highlights raf as a critical effector of ras mediated transformation.

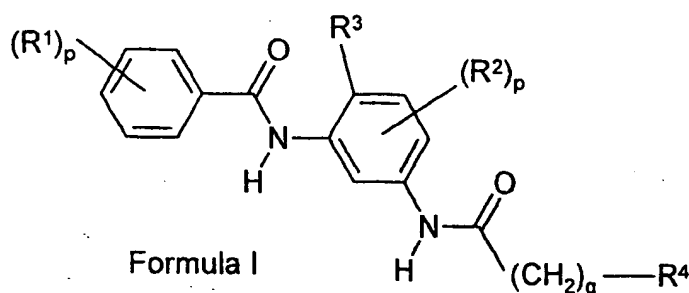
20 Evidence that inhibition of raf will result in anti-tumour activity is set out in the following references.

- 1) Dominant-negative ras mutants block ras function and raf-1 activation by serum or TPA in NIH3T3 cells (Oncogene (1992) 7, 1867-1873).
- 2) Genetic evidence in Drosophila and C. elegans shows that raf is essential for ras
25 stimulated differentiation. (Nature (1993) 360, p600-603; Nature (1993) 363,
133-139).
- 3) Constitutively active mutants of MEK (the downstream target of raf) have been shown to transform NIH3T3 cells (Science (1994) 265, 966-970). Moreover, dominant negative mutants of MEK have been shown to reverse the tumourigenicity of ras transformed cell lines
30 (Cell (1994) 77, 841-852).

- 4) PD098059, a selective inhibitor of MEK activation by raf and other MEK activators (J. Biol. Chem. (1995) 270, 27489-27494) has been shown to block the MAP kinase pathway and reverse the transformation of at least some ras transformed cell lines (Proc. Natl. Acad. Sci. USA (1995) 92, 7686-7689).
- 5) Inhibition of raf function (through use of dominant negative raf or antisense to raf) blocks ras-induced growth or ras-induced reporter gene expression (Nature (1991) 349, 416-428; Genes & Dev. (1992) 6, 545-556).
- 6) Ras antisense has antitumour activity in human tumour mouse xenograft models (Nature Medicine (1996), 2, 668-675).
- 10 Taken together, these findings indicate that raf is both a direct and major effector of ras function and as such inhibition of the kinase activity of raf is expected to have antitumour activity in at least a proportion of human tumours.
- Specific cancers of interest include:
- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary,
 - 15 pancreas, stomach, cervix, thyroid and skin;
 - hematopoietic tumors of lymphoid lineage, including acute lymphocytic leukemia, B-cell lymphoma and Burkett's lymphoma;
 - hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
 - 20 -tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; and
 - other tumors, including melanoma, seminoma, teratocarcinoma, neuroblastoma and glioma.

- Raf inhibitors may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through Ras, e.g.,
- 25 neuro-fibromatosis.

According to one aspect of the present invention there is provided a pharmaceutical composition comprising an inhibitor of raf kinase of the formula I



wherein:

R¹ and **R²**, which may be the same or different are selected from

hydroxy, C₁₋₆alkoxy, mercapto, C₁₋₆alkylthio, amino, C₁₋₆alkylamino,

- 5 di-(C₁₋₆alkyl)amino, carboxy, C₁₋₆alkoxycarbonyl, carbamoyl, C₁₋₆alkylcarbamoyl, di-C₁₋₆alkylcarbamoyl, C₁₋₆alkylsulphonyl, arylsulphonyl, C₁₋₆alkylaminosulphonyl, di-(C₁₋₆alkyl)aminosulphonyl, nitro, cyano, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkanoylamino, C₁₋₆alkoxycarbonylamino, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, C₁₋₆alkyl, halo, trifluoromethyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkoxy, heteroaryl, heteroarylC₁₋₆alkyl,
- 10 heterocyclyl and heterocyclylC₁₋₆alkyl;

p, which may take the same or different values for **R¹** and **R²**, is 0-3, and when **p** is 2 or 3 each group may be the same or different;

R³ is C₁₋₄ alkyl;

q is 0-4;

- 15 **R⁴** is aryl or cycloalkyl wherein **R⁴** is optionally substituted with upto 3 substituents having any value defined for **R¹**;

or a pharmaceutically-acceptable salt or *in vivo* hydrolysable ester thereof and a pharmaceutically-acceptable carrier with the proviso that N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-

- 20 cyclopentylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-phenylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(2-cyclohexylacetyl-amino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-aminobenzamide, N-[5-(3-
- 25 cyclohexylpropionylamino)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxymethylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-

cyclohexylpropionylamino)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-3-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]benzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, are excluded.

The first excluded compound is known as RPR 102359 and is described as upregulating LDL receptors by Brown *et al* in *Atherosclerosis* (1994) 109:113-114. The other excluded compounds are also described as upregulating LDL receptors by Brown *et al* in J. Med. Chem. (1996), 39(17): 3343-3356:

Other compounds within the scope of Formula I are known outside the pharmaceutical field from: Japanese patent 62198852, Nozue *et al.*, Japan Synthetic Rubber Company, Positive-type radiation resist composition; US patent 4410681, Prindle, Dow Chemical Company, Epoxy resins cured with salicyloyl hydrocarbylamines; US patent 4367328, Bertram *et al.*, Dow Chemical Company, Epoxy resins from hydroxybenzamides; Japanese patent JP 53079835, Tanaka *et al.*, Hitachi Limited, Dialkylaminoethyl trimellitate epoxy resin hardeners; German patent DE 2552609, Salle *et al.*, Institut Francais du Petrole, Aromatic diester diamides; Japanese patent JP 50105558, Kubota *et al.*, Adeka Argus Chemical Company, Polymers, hydrocarbon oils and rubbers resistant to metal induced degradation; Japanese patent JP 61204221, Nishizawa *et al.*, Hitachi Chemical Company, Compatible thermosetting epoxy resin compositions; Netherlands patent application 6514411, J R Geigy, Heterocyclic aromatic pigments; and Chem Abs CA 64, 19459g, Tallec *et al.*, Selective reduction of some alkyl-substituted dinitrobenzenes at controlled potential. The reader is directed to these references for general guidance on synthesis of compounds within the scope of Formula I:

"Aryl" in the terms "aryl", "arylC₁₋₆alkyl" and "arylC₁₋₆alkoxy" typically means phenyl or naphthyl, preferably phenyl. "Heteroaryl" in the terms "heteroaryl" and "heteroarylC₁₋₆alkyl" means an aromatic mono- or bicyclic 5-10 membered ring with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur. Examples of 'heteroaryl' include thienyl, pyrrolyl, furyl, imidazolyl, thiazolyl, pyrimidinyl, pyridyl, indolyl, benzimidazolyl, benzothiazolyl, quinolyl and isoquinolyl. "Heterocyclyl" in the terms

"heterocyclyl" and "heterocyclylC₁₋₆alkyl" means a non-aromatic mono- or bicyclic 5-10 membered ring with up to five ring hetero atoms selected from nitrogen, oxygen and sulphur. Examples of 'heterocyclyl' include pyrrolidinyl, morpholinyl, piperidinyl, dihydropyridinyl and dihydropyrimidinyl. "Cycloalkyl" means a non-aromatic mono- or bicyclic 5-10 membered carbon ring. Examples of "cycloalkyl" include cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl and bicyclo[4.4.0]decyl.

Typical values for generic groups include: C₁₋₆alkoxy for example methoxy, C₁₋₆alkylthio for example methylthio, C₁₋₆alkylamino for example methylamino, di-(C₁₋₆alkyl)amino for example dimethylamino, C₁₋₆alkoxycarbonyl for example methoxycarbonyl or ethoxycarbonyl, C₁₋₆alkylcarbamoyl for example methylcarbamoyl, di-C₁₋₆alkylcarbamoyl for example dimethylcarbamoyl, C₁₋₆alkylsulphonyl for example methylsulphonyl, arylsulphonyl for example phenylsulphonyl, C₁₋₆alkylaminosulphonyl for example methylaminosulphonyl, di-(C₁₋₆alkyl)aminosulphonyl for example dimethylaminosulphonyl, cyanoC₁₋₆alkyl for example cyanomethyl, hydroxyC₁₋₆alkyl for example hydroxymethyl, aminoC₁₋₆alkyl for example aminoethyl, C₁₋₆alkanoylamino for example formamido and acetamido, C₁₋₆alkoxycarbonylamino for example methoxycarbonylamino, C₁₋₆alkanoyl for example formyl and acetyl, C₁₋₆alkanoyloxy for example acetoxy, C₁₋₆alkyl for example methyl, ethyl, isopropyl or tert-butyl, halo for example fluoro, chloro or bromo, aryl for example phenyl, arylC₁₋₆alkyl for example benzyl, aryloxy for example phenoxy and arylC₁₋₆alkoxy for example benzyloxy.

Any ring in R¹ or R² may be optionally substituted, for example by upto 3 substituents. Suitable substituents include hydrogen, hydroxy, C₁₋₆alkoxy, mercapto, C₁₋₆alkylthio, amino, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, carboxy, carbamoyl, C₁₋₆alkylcarbamoyl, di-C₁₋₆alkylcarbamoyl, C₁₋₆alkylsulphonyl, arylsulphonyl, C₁₋₆alkylaminosulphonyl, di-(C₁₋₆alkyl)aminosulphonyl, nitro, cyano, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkanoylamino, C₁₋₆alkoxycarbonylamino, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, C₁₋₆alkyl, halo and trifluoromethyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain

alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting raf. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against raf may be evaluated using the standard laboratory techniques referred to hereinafter.

Particular values for R^1 include hydroxy; hydroxy C_{1-6} alkyl for example hydroxymethyl and hydroxyethyl; carboxy; carbamoyl; C_{1-6} alkylcarbamoyl for example methylcarbamoyl and ethylcarbamoyl; di- C_{1-6} alkylcarbamoyl for example di-methylcarbamoyl, di-ethylcarbamoyl and N-ethyl-N-methylcarbamoyl; nitro; cyano;

C_{1-6} alkoxy for example methoxy, ethoxy, propoxy and isopropoxy; amino; C_{1-6} alkylamino for example methylamino, ethylamino and propylamino; di- $(C_{1-6}$ alkyl)amino for example di-methylamino, di-ethylamino and N-ethyl-N-methylamino; and C_{1-6} alkoxycarbonyl for example methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl.

Preferred values for R^1 are hydroxy, amino, C_{1-6} alkylamino, di- $(C_{1-6}$ alkyl)amino, C_{1-6} alkoxy and C_{1-6} alkoxycarbonyl; more preferably hydroxy, methylamino, ethylamino, propylamino, di-methylamino, di-ethylamino and N-ethyl-N-methylamino. Preferred positions for substitution of R^1 into the phenyl ring indicated in Formula I are 3, 4 and/or 5; more preferably 3; 4; 3,4 or 3,5. Favourably R^1 is selected from 4-hydroxy; 4-dimethylamino; 3-methoxy; 3,5-dimethoxy; 3-methoxycarbonyl; and 4-hydroxy-3-methoxy: of these 4-hydroxy is most preferred.

R^2 is preferably hydrogen.

Preferred values for p in $(R^1)_p$ are 1-2, especially 1.

A preferred value for p in $(R^2)_p$ is 0.

Particular values for q are 0-3, 0-2 or 0-1. A preferred value for q is 0.

R^3 is preferably C_{1-3} alkyl, more preferably methyl or ethyl and especially methyl.

R^4 is preferably aryl, more preferably phenyl, more preferably monosubstituted phenyl

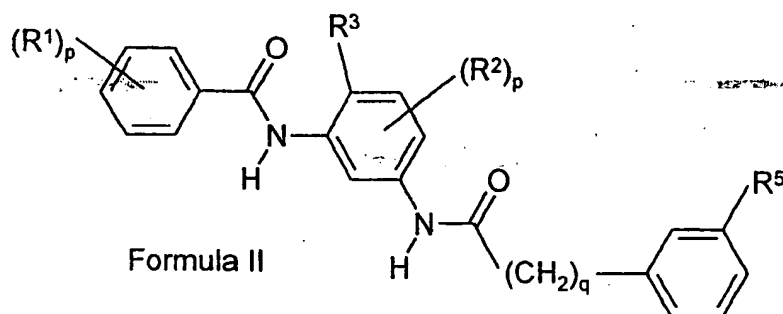
and especially monosubstituted phenyl in the meta position, preferably with an electron withdrawing substituent group. Typical electron withdrawing groups include amino, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, carboxy, C₁₋₆alkylsulphonyl, arylsulphonyl, nitro, cyano, halo, and trifluoromethyl; of these amino, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, nitro, cyano and halo are preferred; more preferably di-(C₁₋₆alkyl)amino; more preferably di-(C₁₋₄alkyl)amino; and especially any of di-methylamino, di-ethylamino and N-ethyl-N-methylamino.

Particular combinations of R¹ and (CH₂)_q-R⁴ include:

R ¹	(CH ₂) _q -R ⁴
4-hydroxy	3-dimethylaminophenyl
4-hydroxy	cyclohexylethyl
4-hydroxy	3,4-dichlorophenylmethyl
4-hydroxy	bicyclo[2.2.1]hept-2-ylmethyl
4-dimethylamino	3-dimethylaminophenyl
3-methoxy	3-dimethylaminophenyl
3,5-dimethoxy	3-dimethylaminophenyl
3-methoxycarbonyl	3-dimethylaminophenyl
4-hydroxy-3-methoxy	3-dimethylaminophenyl

10 and with respect to these combinations, R² is preferably hydrogen and R³ is preferably methyl.

According to another aspect of the present invention there is provided an inhibitor of raf kinase of formula II:



15 wherein:

R¹ and R², which may be the same or different are selected from

hydroxy, C₁₋₆alkoxy, mercapto, C₁₋₆alkylthio, amino, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, carboxy, C₁₋₆alkoxycarbonyl, carbamoyl, C₁₋₆alkylcarbamoyl, di-C₁₋₆alkylcarbamoyl, C₁₋₆alkylsulphonyl, arylsulphonyl, C₁₋₆alkylaminosulphonyl, di-(C₁₋₆alkyl)aminosulphonyl, nitro, cyano, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkanoylamino, C₁₋₆alkoxycarbonylamino, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, C₁₋₆alkyl, halo, trifluoromethyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkoxy, heteroaryl, heteroarylC₁₋₆alkyl, heterocyclyl and heterocyclylC₁₋₆alkyl;

p, which may take the same or different values for R¹ and R², is 0-3, and when p is 2 or 3 each group may be the same or different;

10 R³ is C₁₋₄ alkyl;

q is 0-4;

R⁵ is selected from hydroxy, C₁₋₆alkoxy, mercapto, C₁₋₆alkylthio, amino, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, carboxy, C₁₋₆alkoxycarbonyl, carbamoyl, C₁₋₆alkylcarbamoyl, di-C₁₋₆alkylcarbamoyl, C₁₋₆alkylsulphonyl, arylsulphonyl, C₁₋₆alkylaminosulphonyl, di-(C₁₋₆alkyl)aminosulphonyl, nitro, cyano, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkanoylamino, C₁₋₆alkoxycarbonylamino, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, halo, and trifluoromethyl,

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof with the proviso that methyl 3-[5-(3-methoxycarbonylbenzamido)-2-methylphenyl]aminocarbonylbenzoate is
20 excluded.

In another aspect a preferred individual compound of the invention is N-(5-[2-(3-N,N-dimethylaminophenyl)acetylamino]-2-methylphenyl)-4-hydroxybenzamide or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

Typical and preferred values for (R¹)_p, (R²)_p, R³ and q in Formula II are as set herein in
25 relation to Formula I. R⁵ is preferably an electron withdrawing group. Typical electron withdrawing groups include amino, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, carboxy, C₁₋₆alkylsulphonyl, arylsulphonyl, nitro, cyano, halo, and trifluoromethyl; of these amino, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, nitro, cyano and halo are preferred; more preferably di-(C₁₋₆alkyl)amino; more preferably di-(C₁₋₄alkyl)amino; and especially any of
30 di-methylamino, di-ethylamino and N-ethyl-N-methylamino.

The excluded compound is known from German patent DE 2552609, Salle *et al.*, Institut Francais du Petrole, Aromatic diester diamides.

Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

- 5 a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- 10 c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

In vivo hydrolysable esters are those pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by
15 administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable *in vivo* hydrolysable esters for carboxy include methoxymethyl and for hydroxy include acetyl.

Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the Formula I. An *in vivo* hydrolysable ester of a compound of the Formula I containing a
20 carboxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₆cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-
25 dioxolan-2-ylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

When the compound contains a basic moiety it may form pharmaceutically acceptable salts with a variety of inorganic or organic acids, for example hydrochloric,
30 hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. A suitable pharmaceutically-acceptable salt of the invention when the compound contains an acidic

moiety is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or
5 tris-(2-hydroxyethyl)amine.

In order to use a compound of the Formula I or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

10 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for
15 example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended
20 for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding
25 agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using
30 conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the

active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form
5 together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example
10 heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or
15 condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

20 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be
25 preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.
30 Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

10 Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using 15 one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a 20 suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a 25 conventional, topically acceptable, vehicle or diluent using conventional procedures well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30µm or much less, the powder itself comprising either active ingredient alone or diluted with one or more 30 physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for

use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing
5 finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial
10 Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active
15 agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial
20 Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in
25 treating diseases or medical conditions which are due alone or in part to the effects of raf kinase activity.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be
30 administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will

generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

5 Compounds of this invention may be useful in combination with known anti-cancer and cytotoxic agents. If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

10 Therefore in a further aspect, the present invention provides a compound of the Formula I or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect, the present invention provides a compound of the Formula I or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-cyclopentylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-phenylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(2-cyclohexylacetylamin)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-aminobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxymethylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-3-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]benzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, (hereinafter excluded compounds) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in treating a disease condition mediated by raf kinase.

30 In yet a further aspect the present invention provides a method of treating a disease or medical condition mediated by raf kinase which comprises administering to a warm-blooded

animal an effective amount of a compound of the Formula I or excluded compound or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

The present invention also provides the use of a compound of the Formula I or excluded compound or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof
5 in the preparation of a medicament for use in a disease condition mediated by raf kinase.

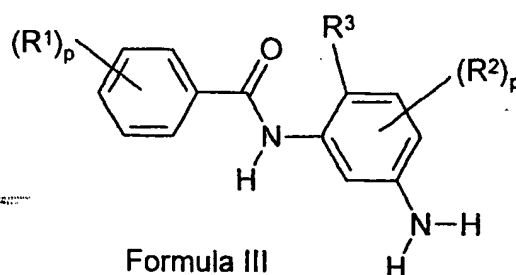
Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of raf kinase. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

10 The compounds of Formula I are especially useful in treatment of tumours having a high incidence of ras mutation, such as colon, lung, and pancreatic tumours. By the administration of a composition having one (or a combination) of the compounds of this invention, development of tumours in a mammalian host is reduced.

In yet a further aspect, the present invention provides a compound of the Formula I or
15 excluded compound or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in the preparation of a medicament for treating cancer.

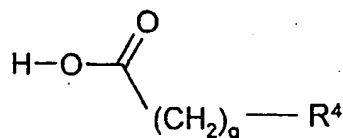
In another aspect the present invention provides a process for preparing a compound of the Formula I or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof which process comprises:

20 reacting a compound of the Formula III:



Formula III

with a compound of the Formula IV



Formula IV

or an activated derivative thereof, under standard amide bond forming conditions, wherein variable groups are as hereinbefore defined wherein any functional group is protected, if necessary, and:

- 5 i. removing any protecting groups;
- ii. optionally forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

Typically a carbodiimide coupling reagent is used in the presence of an organic solvent (preferably an anhydrous polar aprotic organic solvent) at a non-extreme temperature, for example in the region -10 to 40°, typically ambient temperature of about 20°C.

- 10 Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question, and may be introduced by conventional methods.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting
 15 group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" as in, for example, lower alkyl signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples
 20 are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably
 25 containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain C₁₋₁₂alkyl groups (for example isopropyl, *t*-butyl); lower alkoxy lower alkyl groups (for example methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower

alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxy-carbonyloxy lower alkyl groups (for example 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (for example benzyl, *p*-methoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, benzhydryl and phthalidyl);
5 tri(lower alkyl)silyl groups (for example trimethylsilyl and *t*-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (for example trimethylsilylethyl); and C₂₋₆alkenyl groups (for example allyl and vinyllethyl).

Methods particularly appropriate for the removal of carboxy protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

10 Examples of hydroxy protecting groups include lower alkyl groups (for example *t*-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxy-carbonyl groups (for example *t*-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl lower alkoxy-carbonyl groups (for example benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl,
15 *p*-nitrobenzyloxycarbonyl); tri lower alkylsilyl (for example trimethylsilyl, *t*-butyldimethylsilyl) and aryl lower alkyl (for example benzyl) groups.

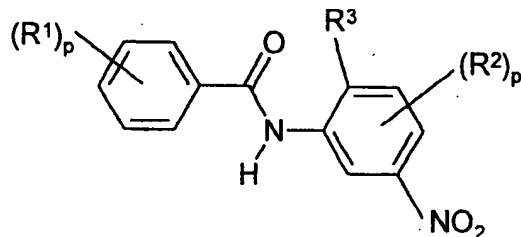
Examples of amino protecting groups include formyl, aralkyl groups (for example benzyl and substituted benzyl, *p*-methoxybenzyl, nitrobenzyl and
20 2,4-dimethoxybenzyl, and triphenylmethyl); di-*p*-anisylmethyl and furylmethyl groups; lower alkanoyl (for example acetyl); lower alkoxy-carbonyl (for example *t*-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl lower alkoxy-carbonyl groups (for example benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl; trialkylsilyl (for example trimethylsilyl and *t*-butyldimethylsilyl);
25 alkylidene (for example-methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis, for groups such as *p*-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as *o*-nitrobenzyloxycarbonyl.

30 The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and

reagents. The reader is referred to Protective Groups in Organic Synthesis, 2nd Edition, by Green *et al.*, published by John Wiley & Sons for general guidance on protecting groups.

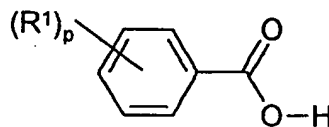
The compound of Formula III may be prepared by reduction of the corresponding nitro compound of Formula V.



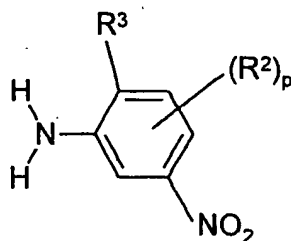
Formula V

Typical reaction conditions include the use of ammonium formate in the presence of a catalyst (for example palladium on carbon) in the presence of an organic solvent (preferably a polar protic solvent), preferably with heating, for example to about 60°. Any functional groups are protected and deprotected as necessary.

The compound of Formula V may be prepared by reaction of a compound of Formula VI with a compound of Formula VII under suitable amide bond forming conditions.



Formula VI



Formula VII

Typical conditions include activating the carboxyl group of the compound of Formula VI for example by treatment with a halo reagent (for example oxalyl chloride) to form an acyl

halide in an organic solvent at ambient temperature, then reacting the activated compound with the compound of Formula VII. Any functional groups are protected and deprotected as necessary.

The following biological assays, data and Examples serve to illustrate the present invention.

Biological Assays

Standard methods for assaying raf activity are described by Alessi *et al.* in Methods in Enzymology Volume 255, 279-290. Particular methods are outlined below.

a) Method for assaying raf activity by means of phosphorylation of MEK

10 Add 2 units active raf enzyme to 2.7 μ g of Glutathione S-transferase MAP/ERK Kinase (GST-MEK), prepared from E. coli by standard procedures, in 30 μ l of 50mM Tris-HCl pH7.4, 0.1mM Ethylene Glycol bis (β -Aminoethylether)NNNN-Tetra-acetic Acid (EGTA), 1mg/ml Bovine Serum Albumin (BSA), 1mM sodium vanadate, 0.03% Brij-35, 0.1% β -mercaptoethanol. Add 10 μ l of inhibitor in 0.1% DMSO. Add 10 μ l of Mg Adenosine
15 Triphosphate (ATP) mix (50mM Mg Acetate, 50 μ M ATP, 1 μ Ci γ^{33} P ATP. Incubate at room temperature for 90 minutes, stop reaction by adding 20 μ l SDS sample buffer and load on Sodium Dodecyl Sulfate (SDS) polyacrylamide gel. Fix the gel, dry and expose to X-ray film or a phosphorimager screen overnight. Phosphorimager analysis allows quantification of the raf activity by measurement of the intensity of the signal from the 70KD GST-MEK band,
20 thus allowing measurement of compound potency against raf.

b) Method for assaying raf activity by means of activating MEK

Method 1

Mix 0.1 units of raf to 0.5 μ g GST-MEK, 1.1 μ g Glutathione S-Transferase Mitogen Activated Protein Kinase (GST-MAP kinase) and 17 μ g myelin basic protein in 30 μ l final
25 volume of 50mM Tris-HCl pH7.4, 0.1mM EGTA, 1mg/ml BSA, 1mM sodium vanadate, 0.03% Brij-35, 0.1% β -mercaptoethanol. Add 10 μ l of inhibitor in 0.1% DMSO. Add 10 μ l of Mg ATP mix (50mM Mg acetate, 150 μ M ATP, 1 μ Ci γ^{33} P ATP. Incubate at room temperature for 90 minutes. Stop the reaction by adding 50 μ l 20% phosphoric acid. Capture onto P81 phosphocellulose paper (Whatman), wash in 0.5% phosphoric acid three times, dry
30 and count by liquid scintillation.

Method 2

Mix 0.02 units of raf to 0.65µg GST-MEK and 2.6µg GST-MAP kinase in 30µl final volume of buffer containing 50mM Tris-HCl pH7.4, 0.1mM EGTA, 1mg/ml BSA, 1mM sodium vanadate, 0.03% Brij-35, 0.1% β-mercaptoethanol. Add 10µl of inhibitor in 0.1% DMSO. Add 10µl of Mg ATP mix (50mM Mg acetate, 1.25mM). Incubate for 60 minutes at room temperature. Transfer 4µl to 50µl of the same buffer containing 17µg myelin basic protein and add 10µl of 50mM Mg acetate, 150µM ATP, 1µCi γ³³P ATP. Incubate at room temperature for 10 minutes. Stop the reaction by adding 50µl 20% phosphoric acid. Capture onto P81 phosphocellulose paper (Whatman), wash in 0.5% phosphoric acid three times, dry and count by liquid scintillation.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

- (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;
- (ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;
- (iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) C18 reverse phase silica separation;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the end-products of the Formula (1) have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and mass spectral techniques; chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t or tr, triplet; m, multiplet; br, broad;
- (vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) or NMR analysis;
- (vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the

end-products of the Formula (1) were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

(viii) the following abbreviations have been used:-

5

DMF dimethylformamide

HPLC high pressure liquid chromatography

MPLC medium pressure liquid chromatography

Example 1**N-[5-(2-Bicyclo[2.2.1]hept-2-ylacetyl-amino)-2-methylphenyl]-4-hydroxybenzamide**

A solution of N-(5-amino-2-methylphenyl)-4-hydroxybenzamide

- 5 (133 mg) in dry DMF (0.5 ml) was added to 2-norbornanylacetic acid (77 mg) followed by a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg) in dry dichloromethane (3.0 ml). The reaction was stirred at ambient temperature for 5 hours. The solvents were removed by evaporation and the residue taken up into ethyl acetate (4.0 ml) and washed with water (3.0 ml). The aqueous layer was back extracted with ethyl acetate (4.0 ml)
- 10 and the combined ethyl acetate extracts were evaporated to give 95 mg (53%) of the title product, shown to be 96% pure by HPLC using the following HPLC System:

Column HYPERSYL ODS 5 μ ; Flow Rate 1.5 ml/min

Dectector Wavelength 280 λ ; Oven Temperature 40 $^{\circ}$ C

Solvent A 1 mmol Et₃N / H₂O; Solvent B 1 mmol Et₃N / CH₃CN

- 15 Time 0-3 min 95%A:5%B

3-17 min gradient to 5%A:95%B

Retention Time 9.58 min.

The starting material was prepared as follows:

- 20 A) Oxalyl chloride (0.5 ml) was added slowly to a stirred suspension of 4-acetoxybenzoic acid (1.09 g), dry dichloromethane (30 ml) and DMF (one drop). The mixture is stirred for two hours at ambient temperature. A solution of 2-methyl-5-nitroaniline (760 mg) and pyridine (2.0 ml) in dry dichloromethane was added over 15 minutes. The reaction mixture was stirred for a further 2 hours, washed with 5% aqueous acetic acid (2 x 25 ml), water (20
- 25 ml) and 5% aqueous sodium hydrogen carbonate solution. The organic extract was dried over magnesium sulphate, filtered and evaporated to dryness. The residue was crystallised from ethyl acetate (100 ml) to give 800 mgs (53%) of 4-acetoxy-N-(2-methyl-5-nitrophenyl)benzamide: melting point 207-208 $^{\circ}$ C.

Microanalysis: % Theory C 61.1, H 4.49, N 8.91

- 30 % Found C 61.0, H 4.3, N 8.8%.

NMR (DMSO-d₆) 2.3 (3H,s); 7.31 (2H,d), 7.56 (1H,d), 8.02 (3H,m); 8.47 (1H,d), 10.12 (1H,s)

MH⁺ = 315

B) A stirred mixture of 4-acetoxy-N-(2-methyl-5-nitrophenyl)benzamide (500 mg), ammonium formate (1.0 g) and 10% palladium on carbon (25 mg) in methanol (10 ml) was heated at 60°C for 2 hours. The reaction mixture was cooled and filtered through diatomaceous earth (Celite®). The filtrate was evaporated to dryness and the residue triturated with water. The crude product was filtered from the aqueous solution and crystallised from methanol to give 140 mg (31% yield) of N-(5-amino-2-methylphenyl)-4-hydroxybenzamide.

Melting point 277-278°C.

10 Microanalysis: C₁₄H₁₄N₂O₂ requires C 69.4, H 5.8, N 11.6%; found C 69.1, H 5.8, N 11.5%.
NMR (DMSO-d₆) 2.03(3H,s); 4.85(2H,s); 6.39(1H,dd); 6.61(1H,d); 6.85(3H,m); 7.82 (2H,d); 9.3(1H,s); 9.96 (1H,s)
MH⁺ = 243

15 Example 2

N-[5-[2-(3,4-Dichlorophenyl)acetylaminol]-2-methylphenyl]-4-hydroxybenzamide

The method of Example 1 was repeated using 3,4-dichlorophenylacetic acid (0.5 mmoles). The reaction mixture was evaporated and the residue taken up in ethyl acetate (4 ml), washed with 1M hydrochloric acid (3.0 ml) and water (3.0 ml). The ethyl acetate extract was evaporated to give the desired product, 132mg (68%), shown to be 92% pure by HPLC.
NMR (DMSO-d₆) δ: 2.23 (s, 3H), 3.73 (s, 2H), 6.93 (d, 2H) 7.23 (d, 1H), 7.35-7.46 (m, 2H), 7.60-7.70 (m, 3H), 7.92 (d, 2H), 9.60 (s, 1H), 10.08 (s, 1H), 10.19 (s, 1H).

Example 3

25 N-[5-(3-Dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide

N-(5-Amino-2-methylphenyl)-4-hydroxybenzamide (85 mg) was added to a stirred solution of 3-dimethylaminobenzoic acid (89 mg) in dry DMF (0.5 ml) followed by a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (103 mg) in dry dichloromethane (3 ml) and 4-dimethylaminopyridine (131 mg). The reaction was stirred at ambient temperature under argon for 18 hours. The reaction mixture was purified by MPLC

on silica eluting in turn with 50%, 60% and 70% ethyl acetate in isohexane to give 17 mg (11%) of the title product.

Microanalysis: % Theory C 68.6, H 5.8, N 10.3 (0.2 CH₂Cl₂)

% Found C 68.1, H 5.7, N 10.9

5 NMR data (DMSO d₆) δ 2.17 (s, 3H); 2.96 (s, 6H); 6.80 - 6.95(m, 3H); 7.15 - 7.35 (m, 4H); 7.58 (dd, 1H); 7.79 (d, 1H); 7.87 (d, 2H); 9.62 (s, 1H), 9.95(s, 1H), 10.10(s, 1H), MH⁺ = 390.

Example 4

10 **Pharmaceutical compositions:**

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

15	(a)	Tablet I	mg/tablet
		Compound X.....	100
		Lactose Ph.Eur.....	182.75
		Croscarmellose sodium.....	12.0
		Maize starch paste (5% w/v paste).....	2.25
20		Magnesium stearate.....	3.0
	(b)	Tablet II	mg/tablet
		Compound X.....	50
		Lactose Ph.Eur.....	223.75
25		Croscarmellose sodium.....	6.0
		Maize starch.....	15.0
		Polyvinylpyrrolidone (5% w/v paste).....	2.25
		Magnesium stearate.....	3.0

30

5	(c) Tablet III	mg/tablet
	Compound X.....	1.0
	Lactose Ph.Eur.....	93.25
	Croscarmellose sodium.....	4.0
	Maize starch paste (5% w/v paste).....	0.75
	Magnesium stearate.....	1.0
10	(d) Capsule	mg/capsule
	Compound X.....	10
	Lactose Ph.Eur.....	488.5
	Magnesium.....	1.5
15	(e) Injection I	(50 mg/ml)
	Compound X.....	5.0% w/v
	1M Sodium hydroxide solution.....	15.0% v/v
	0.1M Hydrochloric acid	
	(to adjust pH to 7.6)	
	Polyethylene glycol 400.....	4.5% w/v
	Water for injection to 100%	
20	(f) Injection II	(10 mg/ml)
	Compound X.....	1.0% w/v
	Sodium phosphate BP.....	3.6% w/v
	0.1M Sodium hydroxide solution.....	15.0% v/v
	Water for injection to 100%	
25		

(g)		Injection III	(1mg/ml, buffered to pH6)
		Compound X.....	0.1% w/v
		Sodium phosphate BP.....	2.26% w/v
		Citric acid.....	0.38% w/v
5		Polyethylene glycol 400.....	3.5% w/v
		Water for injection to 100%	
(h)		Aerosol I	mg/ml
		Compound X.....	10.0
10		Sorbitan trioleate.....	13.5
		Trichlorofluoromethane.....	910.0
		Dichlorodifluoromethane.....	490.0
(i)		Aerosol II	mg/ml
15		Compound X.....	0.2
		Sorbitan trioleate.....	0.27
		Trichlorofluoromethane.....	70.0
		Dichlorodifluoromethane.....	280.0
		Dichlorotetrafluoroethane.....	1094.0
20			
(j)		Aerosol III	mg/ml
		Compound X.....	2.5
		Sorbitan trioleate.....	3.38
		Trichlorofluoromethane.....	67.5
25		Dichlorodifluoromethane.....	1086.0
		Dichlorotetrafluoroethane.....	191.6

(k)	Aerosol IV	mg/ml
	Compound X.....	2.5
	Soya lecithin.....	2.7
	Trichlorofluoromethane.....	67.5
5	Dichlorodifluoromethane.....	1086.0
	Dichlorotetrafluoroethane.....	191.6
(l)	Ointment	ml
	Compound X.....	40 mg
10	Ethanol.....	300 μ l
	Water.....	300 μ l
	1-Dodecylazacycloheptan-2-one.....	50 μ l
	Propylene glycol.....	to 1 ml

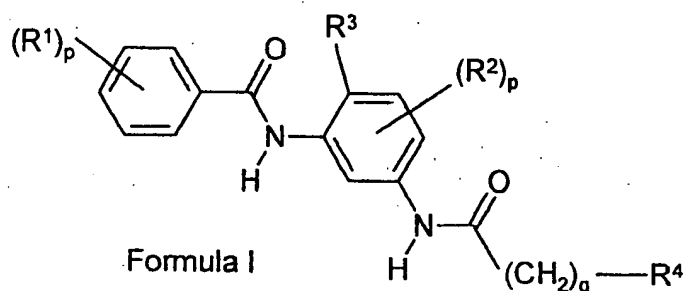
15 Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the

20 suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

Claims

1. A pharmaceutical composition comprising an inhibitor of raf kinase of the formula I



5 wherein:

R^1 and R^2 , which may be the same or different are selected from

hydroxy, C_{1-6} alkoxy, mercapto, C_{1-6} alkylthio, amino, C_{1-6} alkylamino,

di- $(C_{1-6}$ alkyl)amino, carboxy, C_{1-6} alkoxycarbonyl, carbamoyl, C_{1-6} alkylcarbamoyl,

di- C_{1-6} alkylcarbamoyl, C_{1-6} alkylsulphonyl, arylsulphonyl, C_{1-6} alkylaminosulphonyl,

- 10 di- $(C_{1-6}$ alkyl)aminosulphonyl, nitro, cyano, cyano C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkanoylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, C_{1-6} alkyl, halo, trifluoromethyl, aryl, aryl C_{1-6} alkyl, aryl C_{1-6} alkoxy, heteroaryl, heteroaryl C_{1-6} alkyl, heterocyclyl and heterocyclyl C_{1-6} alkyl;

p , which may take the same or different values for R^1 and R^2 , is 0-3, and when p is 2 or 3 each

- 15 group may be the same or different;

R^3 is C_{1-4} alkyl;

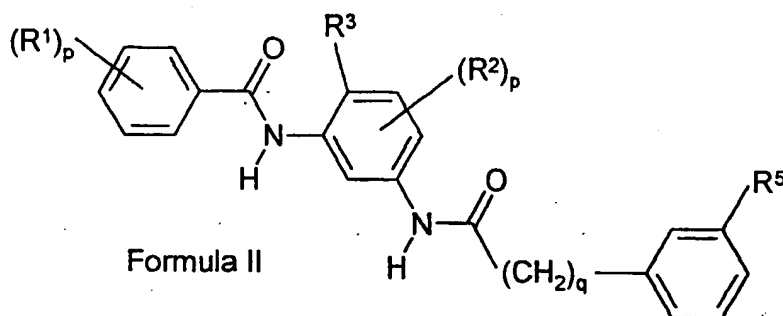
q is 0-4;

R^4 is aryl or cycloalkyl wherein R^4 is optionally substituted with upto 3 substituents having any value defined for R^1 ;

- 20 or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof and a pharmaceutically acceptable carrier with the proviso that N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-cyclopentylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-phenylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(2-cyclohexylacetylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-aminobenzamide, N-[5-(3-

cyclohexylpropionylamino)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxymethylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-3-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]benzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide and N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide are excluded.

- 10 2. A pharmaceutical composition according to claim 1 wherein R³ is methyl.
3. A pharmaceutical composition according to either claim 1 or claim 2 wherein R⁴ is optionally substituted phenyl.
4. A pharmaceutical composition according to any one of claims 1 to 3 wherein p in
15 (R²)_p is 0.
5. A compound of the formula (I) as defined in any one of claims 1 to 4 or a pharmaceutically-acceptable salt or in vivo hydrolysable ester thereof for use as a medicament.
- 20 6. A compound of the formula (I) as defined in any one of claims 1 to 4 or a pharmaceutically-acceptable salt or in vivo hydrolysable ester thereof for use in treating a disease condition mediated by raf kinase.
- 25 7. An inhibitor of raf kinase of formula II:



wherein:

R^1 and R^2 , which may be the same or different are selected from

hydroxy, C_{1-6} alkoxy, mercapto, C_{1-6} alkylthio, amino, C_{1-6} alkylamino,

5 di- $(C_{1-6}$ alkyl)amino, carboxy, C_{1-6} alkoxycarbonyl, carbamoyl, C_{1-6} alkylcarbamoyl, di- C_{1-6} alkylcarbamoyl, C_{1-6} alkylsulphonyl, arylsulphonyl, C_{1-6} alkylaminosulphonyl, di- $(C_{1-6}$ alkyl)aminosulphonyl, nitro, cyano, cyano C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkanoylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, C_{1-6} alkyl, halo, trifluoromethyl, aryl, aryl C_{1-6} alkyl, aryl C_{1-6} alkoxy, heteroaryl, heteroaryl C_{1-6} alkyl,

10 heterocyclyl and heterocyclyl C_{1-6} alkyl;

p , which may take the same or different values for R^1 and R^2 , is 0-3, and when p is 2 or 3 each group may be the same or different;

R^3 is C_{1-4} alkyl;

q is 0-4;

15 R^5 is selected from hydroxy, C_{1-6} alkoxy, mercapto, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di- $(C_{1-6}$ alkyl)amino, carboxy, C_{1-6} alkoxycarbonyl, carbamoyl, C_{1-6} alkylcarbamoyl, di- C_{1-6} alkylcarbamoyl, C_{1-6} alkylsulphonyl, arylsulphonyl, C_{1-6} alkylaminosulphonyl, di- $(C_{1-6}$ alkyl)aminosulphonyl, nitro, cyano, cyano C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkanoylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, halo, and

20 trifluoromethyl,

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof with the proviso that methyl 3-[5-(3-methoxycarbonylbenzamido)-2-methylphenylaminocarbonylbenzoate is excluded.

8. A compound which is

25 N-[5-(2-bicyclo[2.2.1]hept-2-ylacetyl-amino)-2-methylphenyl]-4-hydroxybenzamide;

N-{5-[2-(3,4-dichlorophenyl)acetyl-amino]-2-methylphenyl}-4-hydroxybenzamide;

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide; or
N-{5-[2-(3-N,N-dimethylaminophenyl)acetylamino]-2-methylphenyl}-4-hydroxybenzamide;
 or a pharmaceutically-acceptable salt or in vivo hydrolysable ester thereof.

- 5 9. Use of a compound of the formula (I) as defined in any one of claims 1 to 4 or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-cyclopentylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-phenylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(2-cyclohexylacetyl-
 10 cyclohexylacetyl-
 15 cyclohexylpropionylamino)-2-methylphenyl]-4-aminobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxymethylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-3-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]benzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide
 20 or a pharmaceutically-acceptable salt thereof or an in vivo hydrolysable ester thereof in the preparation of a medicament for treating a disease or medical condition mediated by raf kinase.

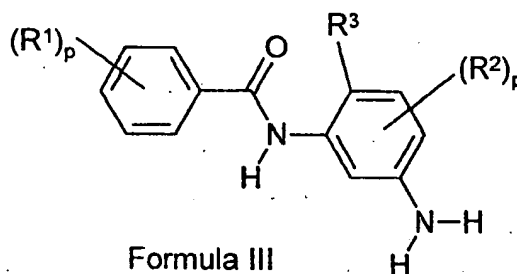
10. Use of a compound of the formula (I) as defined in any one of claims 1 to 4 or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-cyclopentylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-phenylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(2-cyclohexylacetyl-
 25 cyclohexylacetyl-
 30 cyclohexylpropionylamino)-2-methylphenyl]-4-aminobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-

- cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxymethylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-3-hydroxybenzamide,
- 5 N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]benzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide or a pharmaceutically-acceptable salt thereof or an in vivo hydrolysable ester thereof in the preparation of a medicament for treating cancer.
- 10
11. A method of treating a disease or medical condition mediated by raf kinase comprising administering to a warm-blooded animal an effective amount of a compound of the formula (I) as defined in any one of claims 1 to 4 or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-cyclopentylpropionylamino)-2-methylphenyl]-
- 15 4-acetoxybenzamide, N-[5-(3-phenylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(2-cyclohexylacetylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-aminobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-
- 20 cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxymethylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-3-hydroxybenzamide,
- N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]benzamide, N-[5-(3-
- 25 cyclohexylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide,
- or a pharmaceutically-acceptable salt thereof.
12. A method of providing a raf kinase inhibitory effect comprising administering to a warm-
- 30 blooded animal an effective amount of a compound of the formula (I) as defined in any one of claims 1 to 4 or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide,

N-[5-(3-cyclopentylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-phenylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(2-cyclohexylacetyl-amino)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-aminobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxymethylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-3-hydroxybenzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]benzamide, N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-acetoxybenzamide or N-[5-(3-cyclohexylpropionylamino)-2-methylphenyl]-4-hydroxybenzamide, or a pharmaceutically-acceptable salt thereof.

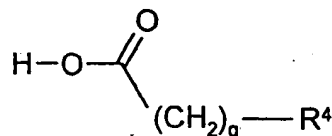
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13. A process for preparing a compound of the formula I or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof which process comprises:
reacting a compound of the Formula III:



20

with a compound of the Formula IV



or an activated derivative thereof, under standard amide bond forming conditions, wherein variable groups are as hereinbefore defined wherein any functional group is protected, if necessary, and:

- i. removing any protecting groups;
- 5 ii. optionally forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/03102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/165 C07C235/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 04170 A (US GOVERNMENT) 4 March 1993 see the whole document ---	11,12
A	ASHTON ET AL.: "New Low-Density Lipoprotein Receptor Upregulators Acting via a Novel Mechanism" J. MED. CHEM., vol. 39, 1996, pages 3343-3356, XP002054111 cited in the application see pages 3344-3345, schemes 1a-4a -----	13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

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Engl, B

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